due to the hydrogen bond formed with the basic nitrogen of 4(3H)-quinazolinone, since mixing with a basic nitrogen such as pyridine, 2,2'-bipyridyl, or quinoline produces a broad band near 3300 cm^{-1}. Interaction of the carbon π-electron system with either the phenolic proton donor or the alcoholic proton could not be observed as a spectral shift in our examinations.

As shown in Table II, 2-(2-pyridyl)-3-phenyl-4(3H)-quinazolinone series seems to be able to function as a proton acceptor more uniquely than III.

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Studies on the Pyridazine Derivatives. XVI.[1] Reaction of 3-Alkoxy-4-nitro-(and 4,6-dinitro)pyridazine 1-Oxides with Amines[2]

Mitsuji Yanai, Toshio Kinoshita, Shigeko Takeda and Hiroshi Sadaki

Faculty of Pharmaceutical Sciences, Nagasaki University[3]

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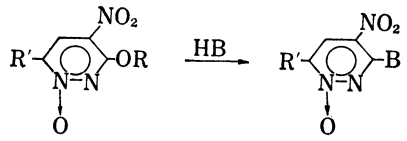
There are several reports on the reaction of alkoxy aromatic amine oxides with amines.[4] The authors attempt the amination of 3-alkoxy-4-nitro(and 4,6-dinitro)pyridazine 1-oxides for the synthesis of 3,4-diamino compounds which are intermediate to imidazo[4,5-*c*]-, *v*-triazolo[4,5-*c*]pyridazines.

General reaction formula of 3-alkoxy-4-nitro(and 4,6-dinitro)pyridazines with amines were shown in Chart 1 and the results were summarized in Table I. Reaction with alcoholic ammonia gave rise to the aminated compounds over 90% yield in any cases. Particularly, dinitro compounds reacted with amines easily. Thus, the present method provides useful synthetic means of triamino compounds. In the reactivity of alkoxy groups, ethoxyl is more active than methoxyl. This tendency is distinct in the reaction with 2-hydroxyethylamine. The reactivity of secondary amines is less active than that of primary amines.



	R	R'
I:	CH_3,	H
II:	CH_3,	NO_2
III:	CH_3,	CH_3
IV:	C_2H_5,	H
V:	C_2H_5,	NO_2

	R'
VI:	H
VII:	NO_2
VIII:	CH_3

HB: a; ammonia b; hydrazine hydrate c; methylamine d; ethylamine e; 2-hydroxyethylamine f; benzylamine g; dimethylamine h; diethylamine i; piperidine j; morpholine

When compound V was treated with dimethylamine under mild condition (at room temperature for one hour), a mixture of 3-dimethylamino-4,6-dinitropyridazine 1-oxide

1) Part XV: M. Yanai, T. Kinoshita and S. Takeda, *Chem. Pharm. Bull.* (Tokyo), **19**, 2181 (1971).
2) This work was presented at Kyushu Branch Meeting of Pharmaceutical Society of Japan, Nagasaki, Sept. 28, 1968.
3) Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*
4) *a*) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 401; *b*) E. Ochiai, *ibid.*, p. 381.

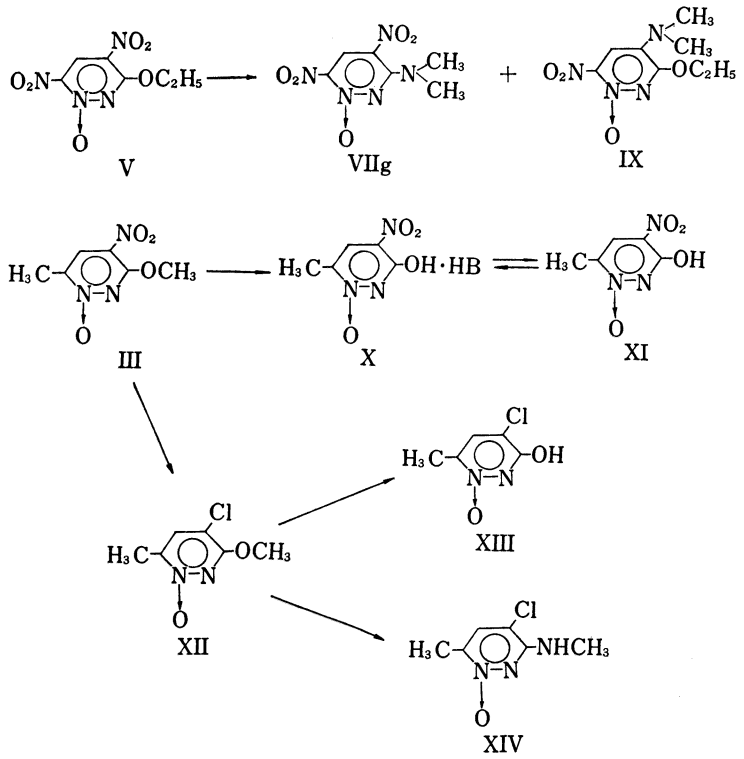


Chart 1

TABLE I

Starting materials No.	R	R′	Amines (HB)	Reaction Temp. (°C)	Time (hr)	Products No.	mp (°C)	Yield (%)	Appearance[a]	Recryst. solvent
IV	Et	H	NH_3[b]	100[c]	1	VIa	246—247	95	Y.P.	water or acetone
I	Me	H	NH_2NH_2[d]	room temp.	2	VIb	185—186	65	B.N.	water
I	Me	H	$NH_2CH_2CH_2OH$[d]	reflux	1	VIe	135.5—136.5	47	O.Pl.	MeOH
IV	Et	H	$NH_2CH_2CH_2OH$[b]	reflux	2/3	VIe	135.5—136.5	60	O.Pl.	MeOH
I	Me	H	$NH_2CH_2C_6H_5$[d]	100[c]	1.5	VIf	200—200.5	83	Y.N.	MeOH
II	Me	NO_2	NH_3[d]	50[e]	1/2	VIIa	209—210[f]	90	Y.P.	MeOH–acetone
V	Et	NO_2	NH_2[b]	50[g]	1/3	VIIa	209—210[f]	94	Y.P.	MeOH–acetone
V	Et	NO_2	aq. NH_2CH_3[d]	50	1/12	VIIc	154—155	60	Y.N.	MeOH
V	Et	NO_2	aq. $NH_2C_2H_5$[d]	50	1/12	VIId	149—150	93	Y.N.	MeOH
II	Me	NO_2	$NH_2CH_2CH_2OH$[d]	reflux	1/2	VIIe	147—148	50	Y.P.	MeOH or EtOH
V	Et	NO_2	$NH_2CH_2CH_2OH$[b]	reflux	1	VIIe	147—148	80	Y.P.	MeOH or EtOH
V	Et	NO_2	$NH_2CH_2C_6H_5$[d]	50	1/6	VIIf	162—163	55	Y.N.	MeOH
V	Et	NO_2	$NH(C_2H_5)_2$[d]	reflux	1	VIIh	153—155	5	Y.P.	AcOEt
V	Et	NO_2	piperidine[d]	reflux	1/2	VIIi	141—142	13	Y.N.	MeOH
V	Et	NO_2	morpholine[d]	reflux	1/2	VIIj	230—231[f]	21	O.R.	EtOH
III	Me	Me	NH_3	140—150[c]	5	VIIIa	203—204.5	59	Y.N.	MeOH
III	Me	Me	NH_2NH_2	room temp.	1	VIIIb	169	64	reddish violet N.	MeOH
III	Me	Me	aq.NH_2CH_3	140—150[c]	5	VIIIc	144—145	56	Y.N.	MeOH
III	Me	Me	$NH_2CH_2CH_2OH$[d]	reflux	1	VIIIe	132—133	67	O.N.	EtOH
III	Me	Me	$NH_2CH_2C_6H_5$	95—100[c]	5	VIIIf	217—218	48	Y.N.	acetone

a) Y: yellow, B: black, O: orange, P: prisms, N: needles, Pl: plates, R: rhombi *b*) in EtOH *c*) in a sealed tube *d*) in MeOH *e*) after in a ice-water 2 hours *f*) decomposition *g*) after in a refrigerator overnight

(VIIg, 10%) and 3-ethoxy-4(or 6)-dimethylamino-6(or 4)-nitropyridazine 1-oxide (IX, 19%) was obtained. The latter is a novel product in comparison with monocyclic aromatic amine N-oxides in which substitution of nitro group with amines is very difficult.[4b] When compound III was treated with primary amines, 3-substituted amino compounds were obtained similar to other nitro compounds, though III was converted with secondary amines into salts (X) which consisted of dealkylated compound XI and corresponding secondary amines in the ratio 1:1. Even primary amines, the salts were obtained in the following cases; i) with aqueous ammonia in a sealed tube and ii) with 2-hydroxyethylamine in a sealed tube. All the salts were decomposed to give 3-hydroxy-4-nitro-6-methylpyridazine 1-oxide (XI) by the acidification with hydrochloric acid, and could be synthesized again from XI and corresponding amines by mere mixing, respectively. Ultraviolet spectra of the salts in 95% ethanolic solution are similar to those of 3-amino-4-nitro compounds. On the other hand, in a solution of 1N hydrochloric acid, the spectra of these salts bear a close resemblance to that of XI.

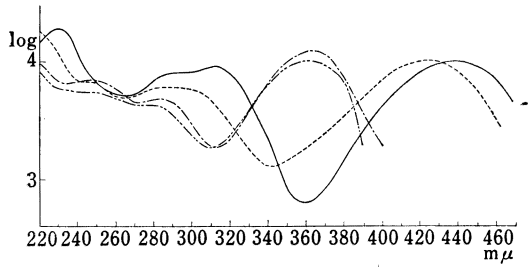


Fig. 1. Ultraviolet Spectra of VIIIc (——: 95% EtOH), Xk (-----: 95% EtOH), XI (—·—: 95% EtOH), and Xk (—·—: 1N HCl)

In order to compare the substituent effects between nitro group and chloro to methoxyl group, the reaction of 3-methoxy-4-chloro-6-methylpyridazine 1-oxide[5] (XII) with methylamine was examined. When XII was treated with 30% aqueous methylamine solution, dealkylated compound (XIII) was obtained in 46% yield. However, the aminated product (XIV) was prepared, as same in case of 3-alkoxy-4-nitro compounds, with methanolic methylamine.

Table II. Ultraviolet Spectra of X and XI

Compound No.	$\lambda_{max}^{95\%\,EtOH}$ mμ (log ε)			$\lambda_{max}^{1N\,HCl}$ mμ (log ε)		
Xe	246 (sh.)[a]	295 (3.70)	428 (3.94)	248 (3.87)	280 (3.74)	363.5 (4.13)
Xg	244 (sh.)	295 (3.42)	428 (3.98)	246 (3.87)	278 (3.75)	364 (4.09)
Xi	245 (sh.)	295 (3.74)	426 (4.03)	245 (3.89)	276 (3.76)	363 (4.06)
Xj	248.5 (3.96)	296 (3.83)	425 (4.04)	248 (3.86)	280 (3.71)	362 (4.09)
Xk	245 (sh.)	294 (3.79)	427 (4.04)	248 (3.75)	280 (3.63)	363 (4.02)
XI	248 (3.85)	284 (3.69)	363 (4.10)			

a) sh.: shoulder

Experimental

General Procedure of 3-Amino-4-nitro Compounds——To a solution of 3-alkoxy-4-nitro compound and MeOH (or EtOH), 1.2—3.8 eq. of amine was added dropwise under stirring and ice cooling (if necessary). The separated crystalline mass was collected and recrystallized from suitable solvent. In the case when crystalline mass did not separate, the reaction mixture was evaporated to dryness *in vacuo* and the residue was then subjected to recrystallization.

Reaction of V with Dimethylamine——A mixture of 1.0 g of V, 2.0 g (4 eq.) of 40% dimethylamine aq. solution and 11 ml of MeOH was allowed to stand at room temperature for 1 hour. The reaction mixture was evaporated to dryness *in vacuo*. The residue was washed with MeOH. The washing was concentrated

5) M. Ogata and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 29 (1963).

Table III

Compounds No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIa	$C_4H_4O_3N_4$	30.78	2.58	35.89	30.51	2.45	35.69
VIb	$C_6H_5O_3N_5$	28.09	2.95	40.93	27.81	2.71	40.48
VIe	$C_6H_8O_4N_4$	36.00	4.03	27.99	35.97	4.00	27.92
VIf	$C_{11}H_{10}O_3N_4$	53.66	4.09	22.76	53.45	4.25	22.36
VIIa	$C_4H_3O_5N_5$	23.88	1.50	34.82	23.87	1.49	34.64
VIIc	$C_5H_5O_5N_5$	27.91	2.34	32.56	28.23	2.57	32.23
VIId	$C_6H_7O_5N_5$	31.45	3.08	30.56	31.63	3.12	30.22
VIIe	$C_6H_7O_6N_5$	29.39	2.88	28.57	29.42	2.76	28.21
VIIf	$C_{11}H_9O_5N_5$	45.36	3.12	24.05	45.13	3.20	23.68
VIIh	$C_8H_{11}O_5N_5 \cdot H_2O$	34.91	4.76	25.45	35.18	4.94	25.49
VIIi	$C_9H_{11}O_5N_5$	40.15	4.12	26.02	40.45	4.23	26.16
VIIj	$C_8H_9O_6N_5$	35.43	3.35	25.83	35.32	3.34	25.46
VIIIa	$C_5H_6O_3N_4$	35.29	3.53	32.94	35.59	3.57	32.26
VIIIb	$C_5H_7O_3N_5$	32.44	3.81	37.83	32.26	3.91	37.93
VIIIc	$C_6H_8O_3N_4$	39.13	4.38	30.42	39.43	4.39	30.07
VIIIe	$C_7H_{10}O_4N_4$	39.26	4.71	26.16	39.45	4.73	25.84
VIIIf	$C_{12}H_{12}O_3N_4$	55.39	4.65	21.53	55.42	4.81	21.19

and the separated crystalline mass was purified by an alumina column chromatography with a mixture of ether and AcOEt, and recrystallized from a mixture of ether and AcOEt to give 0.10 g (10%) of yellow plates, mp 123—124°. *Anal.* Calcd. for $C_6H_7O_5N_5$ (VIIg): C, 31.45; H, 3.08; N, 30.56. Found: C, 31.45; H, 3.25; N, 30.70. Methanol insoluble residue was recrystallized from a mixture of ether and petroleum ether to give 0.19 g (19%) of yellow needles, mp 108—109°. *Anal.* Calcd. for $C_8H_{12}O_4N_4$ (IX): C, 42.10; H, 5.30; N, 24.55. Found: C, 41.70; H, 5.28; N, 24.71.

Reaction of III with aq. Ammonia——A mixture of 3.8 g of III, 30 ml of MeOH and 8 ml of 28% aq. ammonia was heated in a sealed tube at 130—140° for 5 hours. Separated crystalline mass was filtered, washed and recrystallized from MeOH to give 1.45 g (43%) of yellow needles, mp 203—204.5° (This compound was identified with an authentic specimen of XI). The basic filtrate was concentrated and the separated crystalline mass was recrystallized from MeOH to give 0.5 g of yellow needles, mp 265° (decomp.). *Anal.* Calcd. for $C_5H_8O_4N_4$ (Xa): C, 31.92; H, 4.29; N, 29.77. Found: C, 32.09; H, 4.31; N, 29.25.

Reaction of III with 2-Hydroxyethylamine——A mixture of 1 g of III, 8 ml of MeOH and 1 g of 2-hydroxyethylamine was heated in a sealed tube at 100° for 8 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to give 0.08 g (6.4%) of yellow needles, mp 194—195°. *Anal.* Calcd. for $C_7H_{12}O_5N_4$ (Xe): C, 36.21; H, 5.21; N, 24.13. Found: C, 36.02; H, 5.25; N, 23.81.

Reaction of III with Dimethylamine——A mixture of 0.4 g of III, 4 ml of MeOH and 0.5 g of dimethylamine was heated in a sealed tube at 100° for 5 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 0.2 g (43%) of yellow needles, mp 197—198°. *Anal.* Calcd. for $C_7H_{12}O_4N_4$ (Xg): C, 38.89; H, 5.59; N, 25.91. Found: C, 38.88; H, 5.55; N, 25.88.

Reaction of III with Piperidine——A mixture of 0.4 g of III, 5 ml of MeOH and 0.75 g of piperidine was heated in a sealed tube at 140—150° for 5 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from acetone to give 0.28 g (50%) of yellow prisms, mp 149—150.5°. *Anal.* Calcd. for $C_{10}H_{16}O_4N_4$ (Xi): C, 46.88; H, 6.20; N, 21.86. Found: C, 46.99; H, 6.29; N, 21.56.

Reaction of III with Morpholine——A mixture of 0.4 g of III, 5 ml of MeOH and 0.8 g of morpholine was heated in a sealed tube at 140—150° for 5 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 0.32 g (57%) of yellow prisms, mp 194—196°. *Anal.* Calcd. for $C_9H_{14}O_5N_4$ (Xj): C, 41.87; H, 5.46; N, 21.70. Found: C, 42.06; H, 5.34; N, 21.81.

Reaction of III with Bis(2-hydroxyethyl)amine——Bis(2-hydroxyethyl)amine was heated with III under same condition in case of 2-hydroxyethylamine. Yield 44% of yellow needles, mp 121—122°. *Anal.* Calcd. for $C_9H_{16}O_6N_4$ (Xk): C, 39.13; H, 5.84; N, 20.29. Found: C, 39.12; H, 5.72; N, 20.67.

3-Hydroxy-4-nitro-6-methylpyridazine 1-Oxide(XI)——a) X was dissolved in water, acidified with concd. HCl, precipitated crystalline mass was recrystallized from MeOH to give yellow needles, mp 202—203° (decomp.). *Anal.* Calcd. for $C_5H_5O_4N_3$: C, 35.10; H, 2.95; N, 24.56. Found: C, 35.53; H, 2.97; N, 24.38.

b) A mixture of 0.56 g of III and 15 ml of 10% HCl was refluxed for 5 hours, evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 0.2 g of yellow needles, mp 202—203° (decomp.). This compound was identified with the sample obtained above.

Compounds X——A mixture of XI and corresponding amine was heated on a water-bath, evaporated to dryness. The residue was recrystallized from MeOH or EtOH.

3-Hydroxy-4-amino-6-methylpyridazine——XI (1 g) in 200 ml of MeOH was hydrogenated over 0.4 g of 20% Pd-C. The catalyst was filtered, the filtrate was evaporated to dryness. The residue was recrystallized from EtOH to give 0.53 (73%) of colorless cubes, mp 257.5—259°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 48.00; H, 5.64; N, 33.58. Found: C, 48.09; H, 5.61; N, 33.65.

Reaction of 3-Methoxy-4-chloro-6-methylpyridazine 1-Oxide(XII) with Methylamine——a) In an Aqueous Solution: A mixture of 0.5 g of XII, 1.7 g of 30% methylamine and 2 ml of MeOH was heated in a sealed tube at 150—160° for 7 hours. The reaction mixture was evaporated to dryness and the residue was dissolved in $CHCl_3$, poured on an alumina column for chromatography. The solvent was removed to dryness from the elution. To the residue, diluted HCl was added, evaporated to dryness and the residue was recrystallized from EtOH to give 0.21 g of colorless needles, mp 227—228° (decomp.), which was identified with an authentic sample of XIII.

b) In an Ethanolic Solution: A mixture of 0.4 g of XII, 20 ml of ethanolic methylamine was heated in a sealed tube at 150—160° for 7 hours. Solvent was evaporated to dryness, the residue was recrystallized from benzene to give 0.31 g of yellow needles, mp 168—169°. *Anal.* Calcd. for $C_6H_8ON_3Cl$ (XIV): C, 41.50; H, 4.61; N, 24.21. Found: C, 41.45; H, 4.62; N, 24.97.

3-Hydroxy-4-chloro-6-methylpyridazine 1-Oxide(XIII)——A mixture of 0.3 g of XII and 7 ml of 18% HCl was refluxed for 5 hours. Reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from EtOH to give 0.24 g of colorless needles, mp 227.5—228° (decomp.). *Anal.* Calcd. for $C_5H_5O_2N_2Cl$: C, 37.40; H, 3.14; N, 17.45. Found: C, 37.48; H, 3.12; N, 17.50.

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Effects of Phenobarbital, Ethanol and Ethionine on the Content and Fatty Acid Composition of Hepatic Microsomal Phospholipids[1]

Toshihiko Ariyoshi and Eigo Takabatake

Faculty of Pharmaceutical Sciences, Nagasaki University[2]

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The drug metabolizing enzyme activities in the hepatic microsomes were induced by various drugs as well known.[3] The hepatic microsomes consist of fragments of the endoplasmic reticulum and contain higher proportion of phospholipids than any other fraction of cell.[4] The properties of microsomal membrane might be regulated in part by the phospholipid component.[5] The role of phospholipids in the hepatic microsomal drug metabolizing system has been recently investigated in enzymatic or spectral view.[6,7] The content of phospholipid was increased by phenobarbital, a potent inducer of drug metabolizing enzyme.[8]

1) A part of this work was presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
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